

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

11 Publication number:

0 161 898
A2

12

EUROPEAN PATENT APPLICATION

21 Application number: 85303216.7

51 Int. Cl.: **A 61 K 7/16, A 61 K 7/24**

22 Date of filing: 07.05.85

30 Priority: 09.05.84 GB 8411731

43 Date of publication of application: 21.11.85
Bulletin 85/47

84 Designated Contracting States: AT BE CH DE FR GB IT
LI NL SE

71 Applicant: **UNILEVER PLC**, Unilever House Blackfriars
P.O. Box 68, London EC4P 4BQ (GB)

84 Designated Contracting States: GB

71 Applicant: **UNILEVER NV**, Burgemeester
s'Jacobplein 1 P.O. Box 760, NL-3000 DK Rotterdam (NL)

84 Designated Contracting States: BE CH DE FR IT LI NL
SE AT

72 Inventor: **Lane, Roger Michael**, "Underhills" Broad lane,
Heswall Wirral Merseyside (GB)

Inventor: **Hull, Derek Michael Clarke**, 26 Moss Close
Willaston, South Wirral Cheshire (GB)

Inventor: **Saxton, Charles Allan**, 8 Thornton Crescent
Gayton, Wirral Merseyside (GB)

Inventor: **van der Ouderaa, Franciscus J. G.**,
"Kinfauns" 104 Parkgate Road, Neston South Wirral
Cheshire (GB)

74 Representative: **Doucy, Robert Henry et al**, Unilever PLC
Patents Division P.O. Box 68 Unilever House, London
EC4P 4BQ (GB)

54 Dentifrice compositions.

57 It is disclosed that a dentifrice which includes a surfactant and an anti-plaque agent comprising a substantially water-insoluble non-cationic antimicrobial agent or a zinc salt or a mixture thereof has enhanced activity when the dentifrice comprises at least 0.2% by weight of a lamellar liquid crystal surfactant phase having a lamellar spacing of less than 6.0 nm.

EP 0 161 898 A2

DENTIFRICE COMPOSITIONS

5 This invention relates to dentifrice compositions,
more particularly to dental creams or gels, for
inhibiting the formation of dental plaque.

10 It is now established that there is a relationship
between dental plaque and gingival inflammation. At
present, mechanical cleaning by toothbrushing is the most
widely used method of removing plaque. However, the
relatively short period of brushing commonly practised is
insufficient to achieve adequate removal of plaque
especially from areas least accessible to brushing.

15 The dental literature over the last 25 years is
replete with publications concerned with the use of
organic antimicrobial agents to combat dental plaque.
Most work has concentrated on the use of cationic agents
20 because these are substantive to oral tissues and are
therefore retained in the mouth. It is believed that their
activity is due to their being adsorbed onto oral surfaces

and gradually released over a period of time (Journal of Clinical Periodontology 1980: 7 431-442). Unless an active antimicrobial agent is adsorbed onto oral surfaces the oral bacteria in the mouth rapidly recover and no
5 significant reduction in plaque growth would be expected (British Dental Journal March 1984, 175-178). However, the successful formulation of a cationic antimicrobial agent into a commercially acceptable toothpaste has not yet been achieved and this is at least
10 in part due to the incompatibility of cationic antimicrobial agents with common toothpaste ingredients. In addition, cationics, especially chlorhexidine which has been extensively investigated, have the further
15 disadvantage of causing tooth staining as well as having a long-lasting bitter taste. Many cationics also cause irritation of the oral tissues. Attempts to overcome the tooth staining problem are the subject of many patents. We believe that there is to date no commercial toothpaste
20 containing an organic cationic antimicrobial agent which is recognised as having a significant anti-plaque benefit.

Although there are references in the literature to attempts to use antimicrobial agents other than cationic
25 compounds for providing an improvement in oral health it is generally considered that the oral substantivity of these agents is not sufficient to provide a significant antiplaque benefit and they are in any case considered unattractive because of their generally poor
30 water-solubility. Hitherto it has been the general belief that it is necessary for the active agent of a dentifrice to be in solution in the aqueous phase of the toothpaste.

35 . We have now discovered that it is possible to obtain substantial reductions in plaque growth by means of a

substantially water-insoluble non-cationic antimicrobial agent, or mixture of antimicrobial agents, provided the dentifrice composition containing it has certain characteristics of which details are given below. Such
5 unexpected anti-plaque activity we believe is due to the fact that the special dentifrice composition of the invention is able to deliver the antimicrobial agent to tooth surface where it is retained for a time sufficient to materially affect the rate of plaque regrowth, rate of
10 plaque metabolism and equilibrium plaque level.

Our research has also shown that our special dentifrice composition is also able to lead to an enhanced retention in the mouth of zinc salts, generally known to
15 have an anti-plaque effect, resulting in an improvement in effectiveness in inhibiting plaque growth. Various zinc salts, for example zinc citrate, are referred to in US-A-4 022 880. The use of zinc
carboxymethyloxysuccinate is referred to in
20 US-A-4 144 323.

According to the present invention there is provided a dentifrice composition effective to inhibit the growth of dental plaque comprising a surfactant and an
25 anti-plaque agent consisting of a substantially water-insoluble non-cationic antimicrobial agent or a zinc salt having a water solubility greater than 2×10^{-4} g, preferably greater than 1×10^{-2} g, per 100g of water at 25°C and at pH7, or a mixture thereof, characterised in that
30 there is present in the dentifrice composition a lyotropic lamellar liquid crystal phase comprising alternate layers of surfactant molecules and water molecules (and hereinafter referred to as a lamellar liquid crystal
surfactant phase) having a lamellar spacing of less than
35 6.0 nm, the lamellar liquid crystal surfactant phase being present in an amount of at least 0.2%, preferably at least

0.3%, and more preferably at least 0.5%, by weight of the dentifrice composition.

5 The determination of whether a dentifrice composition comprises a lamellar liquid crystal surfactant phase can be determined by examination of the product obtained by subjecting the dentifrice to a centrifuge separation procedure, which will now be described.

10 The dentifrice is centrifuged with sufficient centrifugal force to separate the main phases present which usually are abrasive, aqueous, detergent and flavour phases. A preliminary centrifugation is
15 convenient to separate the majority of the abrasive, followed by an ultracentrifugation to separate the phases of the liquid portion. The speed and duration of the centrifugation required is dependent upon the resistance of the formulation towards separation. The separation of
20 a dentifrice containing sodium carboxymethylcellulose as binder is facilitated by degrading the binder enzymatically prior to centrifugation. The dentifrice is incubated with cellulase-containing powder (0.1% w/w, prepared from *Aspergillus niger*, activity 1.3 units/mg) for 18 hours at room temperature to degrade the sodium
25 carboxymethylcellulose binder.

The resultant slurry or the dentifrice itself, if no preliminary degradation of the binder is carried out, is centrifuged at 10,000xg for 1 hour and the sedimented
30 abrasive removed. The liquid portion is then ultracentrifuged at 200,000xg for 2 hours or until there is no substantial change in the volumes of the separated layers. These conditions of centrifugation have
generally been found to be satisfactory for separating the
35 phases of a dentifrice although longer periods of

centrifugation and ultracentrifugation may sometimes be necessary.

5 The product obtained by this centrifuge procedure is referred to herein as the centrifuge separation product. The centrifuge separation product will consist of a number of layers. The lower layer of solids and the humectant-containing layer above it will together constitute the major part of the centrifuge separation
10 product. The remainder of the centrifuge separation product may include a layer consisting predominantly of surfactant in the form of liquid crystals. If present, this layer will generally constitute the upper layer or one of the upper layers. Its actual position will
15 depend on the relative densities of the layers. This layer constituting the liquid crystal surfactant phase of the dentifrice can be removed from the centrifuge separation product and its weight as a percentage of the dentifrice determined. The lamellar liquid crystal
20 surfactant phase is basically made up of layers of surfactant molecules separated by water layers but may comprise other components depending upon the overall composition of the dentifrice. The distribution of such other components between the surfactant and water layers
25 will depend upon their respective aqueous solubilities and hydrophobicities.

 Liquid crystals are well known and a recent book describing them is entitled "Aggregation Processes in
30 Solution" edited by E Wyn-Jones and J Gormally published by Elsevier Scientific Publishing Company, Amsterdam-Oxford-New York 1983, and particular reference is made to Chapter 7 entitled "Lyotropic Liquid Crystals".

35 If the centrifuge separation product comprises a lamellar liquid crystal surfactant phase then the layer

spacing can be determined by an X-ray scattering technique.

The layer spacing, d_o , is defined as the distance
5 between repeat units in the cross-section of a layered
liquid crystal structure, ie. the combined thickness of
the detergent sheet and of the water layer sandwiched
between the detergent sheets. It can be measured by
Small Angle X-ray Scattering (SAXS), a technique used to
10 determine long periodicities in the range 1 nm-1,000 nm in
crystalline or liquid crystal materials. The 'Kratky'
SAXS camera used in such work produces, through a
sophisticated collimation system, a fine beam of X-rays
(Cu, K_{α} radiation) which impinge on the sample contained
15 in a 1 mm glass capillary or sandwiched between 6 μ thick
Mylar film.

The scattered radiation is detected by a proportional
counter which determines the variation in scattered
20 intensity with respect to angle. The angle corresponding
to the peak maximum is measured from the chart recorder
trace and the corresponding 'd-spacing' is calculated from
Bragg's equation

$$25 \quad 2d \sin \theta = n\lambda$$

with $n = 1$, $\lambda = 0.1542$ nm for Cu K_{α} radiation.

Applications of this technique for the measurement of
the lamellar spacing of lamellar liquid crystal phases are
30 described in Journal of Colloid and Interface Science,
Vol. 41, No. 1, April 1974, pages 59 to 64 and Vol. 86,
No. 2, April 1982, pages 501 to 514.

The lamellar spacing of the liquid crystal surfactant
35 phase of a dentifrice according to the present invention

is preferably less than 5.0 nm, more preferably less than 4.4 nm.

Dentifrices usually comprise an anionic surfactant and most commonly used is sodium lauryl sulphate derived from coconut fatty acids comprising mainly sodium dodecyl sulphate, although pure sodium dodecyl sulphate can be used. Sodium dodecylbenzene sulphonate is another known dentifrice surfactant although it is not usually employed as the sole surfactant of a dentifrice. It may be used in combination with sodium lauryl sulphate. Suitable combinations of sodium lauryl sulphate and sodium dodecyl benzene sulphonate are in the proportions 4:1 to 1:4 by weight. The use of a combination of these surfactants in a dentifrice comprising a zinc-containing anti-plaque agent is described in GB-A-1 373 003. Sodium lauroyl sarcosinate is another well-known dentifrice surfactant that may also be employed in dentifrices of this invention.

20

The surfactant in a dentifrice can be present in three main forms, as a solution, a liquid crystal phase or crystalline solid. The form or forms in which the surfactant is present depends particularly on the other ingredients of the dentifrice. Thus in the presence of glycerol, which is very commonly used as the sole or major humectant liquid, the surfactant will generally be present as a solution since glycerol is a solvent for common dentifrice surfactants. The same applies to propylene glycol, also a well-known dentifrice humectant. We have also found that when sorbitol is employed as the humectant then in the absence of a flavour oil the surfactant is present as a solid crystalline phase due to its poor solubility in sorbitol solution. However, in the presence of flavour oil the solid crystalline surfactant phase is converted into a lamellar liquid crystal phase.

35

Thus dentifrice formulations that promote the formation of a liquid crystal surfactant phase are those based on the use of sorbitol as the humectant and which also contain a flavour oil. However, the use in combination with sorbitol of such amounts of glycerol that do not prevent the formation of a liquid crystal surfactant phase is permissible. Other ways of producing a lamellar liquid crystal surfactant phase are, of course, within the scope of the present invention.

10

The layer spacing of a liquid crystal surfactant phase in a dentifrice is influenced by the electrolyte concentration of the aqueous phase. Thus the obtaining of a layer spacing of less than 6.0nm in accordance with this invention can be effected by control of the electrolyte concentration of the aqueous phase. In order to achieve such a low lamellar spacing the electrolyte concentration needs to be relatively high. However, means other than control of electrolyte concentration may be employed to control lamellar spacing.

20

An appropriate concentration of the electrolyte can be produced by the addition of a suitable water-soluble electrolyte. Only simple experimentation is required to determine the amount of electrolyte required to give a low d_0 value. In general, any non-toxic salt or mixture of salts that is compatible with the therapeutic ingredient or ingredients, as well as with the other dentifrice components, and is organoleptically acceptable can be used. The salt that is referred to here is in addition to any fluorine-containing salt which may be included to give an anti-carries benefit. Such salt is of course, in addition to the surfactant (which is also an electrolyte) and any zinc salt which may also be present. The additional salt is also to be distinguished from a binder or thickener for the aqueous humectant liquid phase, said

25

30

35

binder or thickener being a commonly employed dentifrice ingredient and which may be constituted by a salt, eg sodium carboxymethylcellulose. The surfactant, binder and fluorine-containing salts when employed at
5 conventional levels do not produce, even in combination, a sufficient concentration of electrolyte to reduce the layer spacing of a surfactant liquid crystal phase to below 6.0nm.

10 The cation of the added salt is preferably sodium, potassium, aluminium, magnesium or zinc. Suitable anions are acetate, chloride, citrate, gluconate, lactate, sulphate, phosphate, tartrate, glyconate and ascorbate. Some salts are more effective than others in reducing the
15 d_o value at the same molar cation addition. Preferred salts are those of sodium and aluminium.

We have found that the amount of sodium chloride added is suitably in the range from about 0.1 to about 3%,
20 preferably about 0.1 to about 1%, by weight of the dentifrice composition. Other salts may be added in such amounts that the total cation molar concentration corresponds to those for sodium chloride previously given.

25 It is not advisable to include any more salt than is necessary to produce the desired low lamellar spacing. Excessive amounts may not only impair the organoleptic qualities of the dentifrice but in fact will result in the destruction of the liquid crystal phase. We have found
30 that a liquid crystal surfactant phase may be destroyed on the addition of 5% sodium chloride. Consequently, it is recommended that the amount of any added electrolyte should not exceed the cation molar equivalent of about 3% by weight of the dentifrice of sodium chloride. In
35 practice, an optimum reduction in layer spacing can be

achieved at levels of addition of sodium chloride substantially less than 3% by weight.

5 A zinc salt, if present, will contribute to the total electrolyte concentration of the aqueous phase.

10 A part of the electrolyte present in the aqueous phase may be composed of ions originating from a solid abrasive agent, for example aluminium ions from an alumina abrasive, and the proportion of such ions in the aqueous phase can be dependent upon the type of mixer employed, more especially upon the energy employed in mixing the solid components during the manufacture of the dentifrice.

15 The dentifrices of this invention generally have a weight of liquid crystal surfactant phase of at least 1% and they typically have a content thereof of from 1.5 to 12% by weight.

20 The antiplaque agent of the dentifrice of the invention is a substantially water-insoluble non-cationic antimicrobial agent or a zinc salt as defined above or a mixture thereof. By a substantially water-insoluble antimicrobial agent is meant herein one having a
25 solubility in water at 25°C of less than 1%, preferably less than 0.5% and more preferably less than 0.1%, save that if the antimicrobial agent contains ionisable groups the solubility is determined at a pH at which such groups are not ionised. The antimicrobial agents employed in
30 dentifrice compositions of this invention can be regarded as essentially non-ionic in character. However, many suitable antimicrobial compounds contain one or more phenolic hydroxy groups which may be ionisable at certain pHs and therefore it is considered more exact to describe
35 the general class of antimicrobial agents useful in the

dentifrice composition of this invention as being non-cationic in nature.

5 Examples of classes of non-cationic antimicrobial agents which may be employed in the dentifrice composition of the invention are the phenolic and bisphenolic compounds, halogenated diphenyl ethers, benzoate esters and carbanilides.

10 Illustrative of the phenolic antimicrobial compounds, which include the halogenated salicylanilides, are

2-phenylphenol
4-chlorophenol
15 4-chloro-2-methylphenol
4-chloro-3-methylphenol
4-chloro-3,5-dimethylphenol
2,4-dichloro-3,5-dimethylphenol
3,4,5,6-tetrabromo-2-methylphenol
20 5-methyl-2-pentylphenol
4-isopropyl-3-methylphenol
5-chloro-2-hydroxydiphenylmethane
4',5-dibromosalicylanilide
3,4',5-trichlorosalicylanilide
25 3,4',5-tribromosalicylanilide
2,3,3',5-tetrachlorosalicylanilide
3,3',4,5'-tetrachlorosalicylanilide
3,5-dibromo-3'-trifluoromethylsalicylanilide
5-n-octanoyl-3'-trifluoromethylsalicylanilide

30

Among the bisphenolic compounds may be mentioned

2,2'-methylenebis(3,4,6-trichlorophenol)
2,2'-methylenebis(4-chlorophenol)
35 2,2'-methylenebis(4-chloro-6-bromophenol)

bis(2-hydroxy-3,5-dichlorophenyl) sulphide
bis(2-hydroxy-5-chlorophenyl) sulphide.

5 These antibacterial agents may be employed in the
form of their zinc derivatives many of which are disclosed
in US-A-4 022 880.

Exemplifying the class of the halogenated
hydroxydiphenyl ethers are the compounds
10 2',4,4'-trichloro-2-hydroxy-diphenyl ether and
2,2'-dihydroxy-5,5'-dibromo-diphenyl ether.

[Another well-known class of non-cationic]
antimicrobial agents are the esters of p-hydroxybenzoic
15 acid, especially the methyl, ethyl, propyl, isopropyl,
butyl, isobutyl, hexyl, heptyl and benzyl esters. x

Halogenated carbanilides can also be used, which
class is typified by
20

3,4,4'-trichlorocarbanilide
3-trifluoromethyl-4,4'-dichlorocarbanilide
3,3',4-trichlorocarbanilide

25 Other known substantially water-insoluble
non-cationic antimicrobial agents can also be used, for
example 2,4-dichlorobenzyl alcohol, 3,4-dichlorobenzyl
alcohol and 3-(4-chlorophenoxy)-propan-1,2-diol.

30 The preferred antimicrobial agents are halogenated
bisphenolic compounds, and the halogenated hydroxydiphenyl
ethers. Especially preferred are
2',4,4'-trichloro-2-hydroxy-diphenyl ether (hereafter
referred to as Triclosan) and 2,2'-methylene
35 bis(4-chloro-6-bromophenol).

The above-mentioned antimicrobial agents which are suitable for use in dentifrices are not antibiotics. Antibiotics are not generally used so as to avoid the risk of resistant strains of bacteria developing.

5

The antimicrobial agent will usually be used in an amount of 0.01 to 5%, preferably 0.05 to 1% by weight of the dentifrice. A mixture of antimicrobial agents may of course be used.

10

The anti-plaque agent of the dentifrice composition of the invention alternatively may be a zinc salt having a water solubility greater than 2×10^{-4} g, preferably greater than 1×10^{-2} g, per 100g of water at 25°C and at pH7. Many suitable zinc salts are described in US-A-4 022 880. Preferred zinc salts are those of mono-, di- and tri-carboxylic acids, alpha-hydroxy carboxylic acids and amino acids. Examples of preferred salts are zinc citrate, zinc tartrate, zinc malate, zinc lactate, zinc glycinate, zinc glycolate, zinc succinate, zinc carboxymethyloxysuccinate, zinc gluconate, zinc salicylate, zinc histamine and zinc histidine. Ammonium and alkali metal zinc citrates as described in US-A-4 325 939 may also be used. More than one zinc salt can be of course be employed.

25

The zinc salt, or mixture of zinc salts, is desirably used in an amount such as to provide in the dentifrice from about 0.05 to about 1.5% by weight of zinc.

30

The preferred zinc salt is zinc citrate. This is readily available as the trihydrate. This is preferably incorporated in an amount of about 0.2 to about 5% by weight, and for best organoleptic acceptability most preferably 0.2 to 2% by weight.

35

Best results are obtained by using an antimicrobial agent in combination with a zinc salt, such as zinc citrate. Most preferred antiplaque systems are based on the combination of Triclosan and zinc citrate and the combination of 2,2'-methylenebis(4-chloro-6-bromophenol) and zinc citrate. Combinations of an antimicrobial agent and zinc citrate give the best degree of plaque growth inhibition, the most preferred combination being that of Triclosan and zinc citrate. With the latter combination a plaque inhibition approaching that obtainable with chlorhexidine has been obtained without the severe drawbacks associated with the use of that cationic material.

A particularly preferred dentifrice composition according to the invention comprises 0.05 to 0.3% Triclosan, 0.3% to 1.5% zinc citrate, 0.2 to 1% sodium chloride and 1 to 3% sodium lauryl sulphate.

The dentifrice composition of the invention preferably also comprises a particulate abrasive agent compatible with the active ingredients of the toothpaste. Especially preferred are hydrated alumina and silica abrasives, both of which are widely employed in commercial products. The particle size of the abrasive agent will usually be in the range 2 to 20 microns as is customary. Suitable grades of alpha-alumina trihydrate are sold under the name BACO by BA Chemicals of Great Britain and under the name MARTINAL by Martinswerke GmbH of Germany. Preferred silica abrasives are the well-known silica xerogels, for example GASIL 200 (sold by Crosfield Chemicals, Great Britain) and SYLOID 63 (sold by Grace Corporation USA), and precipitated silicas, for example ZEO 49 (sold by the Huber Corporation USA). The amount of abrasive agent employed will usually be between 5 and 60% by weight of the dentifrice composition.

Suitable binders or thickeners for use in dentifrice compositions are known to those skilled in the art. Commonly used are sodium carboxymethylcellulose and xanthan gum. For flavouring dentifrices peppermint and spearmint oils are commonly used, although a wide variety of other oils also find application. Flavour oils are usually present in an amount of from 0.1 to 5% by weight. Apart from the above generally standard ingredients, a number of optional ingredients may also be included, especially fluoride, such as sodium monofluorophosphate or sodium fluoride, , opacifying agent, eg titanium dioxide, preservative, sweetening agent and a pH-adjusting agent.

The water content of the dentifrices in accordance with this invention will generally be between about 25 and 60% by weight of the dentifrice excluding insoluble solids. Sorbitol, as 70% solution, typically amounts to 10-70% by weight of the dentifrice.

The dentifrices of the invention can be made by conventional methods. Since the obtaining of a low d_o spacing of a liquid crystal surfactant phase is controlled by the concentration of the electrolyte in the aqueous phase of the final toothpaste composition, water loss during manufacture affects the electrolyte concentration. It is therefore desirable to avoid the use or production of excessive temperatures during manufacture and preferably the temperature of processing is within the range 15 to 35°C, more preferably 22 to 32°C.

The present invention in one aspect relates to a process for making a dentifrice composition which includes added sodium chloride or other water-soluble salt, which process comprises mixing the water-soluble salt with the other ingredients so as to result in an aqueous phase having an electrolyte concentration sufficient to result in the formation of a liquid crystal surfactant phase

having a lamellar spacing of less than 6.0 nm, the dentifrice ingredients preferably being mixed at a temperature within the range 15 to 35°C, more preferably 22 to 32°C.

5

The following Examples illustrate the invention. Percentages are by weight.

Example 1

10

A number of toothpastes were made from the following ingredients.

	<u>Ingredient</u>	<u>%</u>
15	Alumina trihydrate	50.000
	Sorbitol syrup (70% solution)	27.000
	Sodium lauryl sulphate	1.875 ^{II}
	Sodium dodecylbenzenesulphonate	0.625
	Sodium carboxymethylcellulose	0.800
20	Zinc citrate trihydrate	1.000
	Triclosan	0.500
	Sodium monofluorophosphate	0.850
	Flavour oil	1.200
	Sodium saccharinate	0.180
25	Formalin BP	0.040
	Water	to 100.000

The toothpastes were made using a variety of toothpaste mixers some mixers having a greater energy of mixing than others. In some cases there was more water loss than others. This together with differing amounts of cations from the abrasive which passed into solution resulted in the toothpastes having differing electrolyte concentrations. In each case the surfactant was present in the toothpaste in the form of a liquid crystal phase but the lamellar spacings were different for the different

toothpastes as a consequence of the differing electrolyte concentration of the aqueous phase of the final products. In the manufacture of the toothpastes of this Example, and of those of all subsequent Examples, the ingredients are mixed at a temperature within the range 22 to 32°C. The values for the lamellar spacing, d_o , are given in Table I below. These values, and all other d_o values given herein, are those determined within a month of manufacture of the respective toothpaste.

10

Also given in Table I are PG values for the respective products. PG stands for Plaque Growth and the smaller the PG value the greater the efficacy of the toothpaste to inhibit the growth of plaque on the teeth. The PG value is determined from data obtained when following a standard procedure for the measurement of plaque growth. The methodology of measuring plaque growth is that according to Harrap as described in J.Clin.Periodontol., 1974, 1, 166-174 which gives a procedure for assessing the amount of plaque on the teeth adjacent to the gingival margin. The procedure is as follows:

During the late afternoon each subject brushes his teeth with a simple, non-active paste (having a composition as given hereinafter) for an unspecified period of time to remove as much plaque as possible. This is immediately followed by brushing for one minute with 1.5g of the allocated test paste. Residual paste is removed by rinsing the mouth with water and any remaining plaque disclosed by painting the teeth with an aqueous solution of Erythrosin (0.5% w/w) using a soft camel hair brush. Excess dye is removed by rinsing with water and the amount of plaque assessed and recorded for each of 16 teeth (numbers 3 to 6 for each quadrant). The recorded plaque is designated P_o .

No further oral hygiene is permitted for 18 hours after which time each subject rinses his mouth with water to remove food debris and viscous saliva. Plaque assessment is then carried out as before and recorded (P₁₈). The values of P₁₈-P₀ for each tooth are averaged to give a P₁₈-P₀ value per mouth. The mean of the values obtained for the subjects in the test is the PG value. Panels of at least 12 subjects are used. The Plaque Growth value for a toothpaste without active ingredients is usually in the range 22 to 26.

The composition of the simple, non-active toothpaste referred to above was the following:-

15	<u>Ingredient</u>	<u>%</u>
	Alumina trihydrate	50.00
	Glycerin	27.00
	Hydroxyethylcellulose	0.95
	Titanium dioxide	0.50
20	Water	to 100.00

The lamellar spacings and PG values for the toothpastes that were formulated are presented in Table I in the order of the magnitude of the lamellar spacings.

TABLE I

5	<u>Lamellar spacing of Liquid</u>	<u>PG</u>
	<u>Crystal Surfactant Phase (nm)</u>	<u>Value</u>
	6.6	19.9
	6.3	18.5
	6.1	16.8
10	5.6	16.1
	5.0	15.6
	4.8	14.5
	4.6	13.4
	4.3	12.4
15	4.0	12.0

This shows that as the d_o value decreases the effectiveness of the toothpaste in inhibiting plaque growth increases.

20

The amounts of the liquid crystal surfactant phase for the above toothpastes all exceeded 1.5% by weight of the respective toothpaste.

25 Example 2

This example shows the beneficial decrease in the PG value that can be obtained by the addition of a relatively minor amount of electrolyte.

30

Various toothpastes containing sodium chloride were made employing the ingredients listed in Table II.

TABLE II

	<u>Ingredient</u>	Toothpaste: <u>A</u>	<u>B</u>	<u>C</u>
5				
	Alumina trihydrate	50.000	50.000	50.000
	Sorbitol syrup (70%)	27.000	27.000	27.000
	Sodium lauryl sulphate	1.875	1.875	1.875
	Sodium dodecylbenzene			
10	sulphonate	0.625	0.625	0.625
	Sodium			
	carboxymethylcellulose	0.850	0.850	0.800
	Zinc citrate trihydrate	0.500	0.500	0.500
	Triclosan	0.200	0.200	0.200
15	Sodium chloride	0.500	0.500	0.500
	Titanium dioxide	0.500	-	-
	Sodium			
	monofluorophosphate	0.850	0.850	0.850
	Sodium saccharin	0.180	0.180	0.180
20	Formalin BP	-	0.040	0.040
	Flavour oil	1.200	1.200	1.200
	Water	to 100.000	100.000	100.000

Corresponding toothpaste A', B' and C' were made from
 25 which the sodium chloride was omitted.

The toothpastes of each pair of toothpastes A A',
 B,B'and CC' were made in an identical manner using the
 same mixer. The respective pairs were manufactured using
 30 commercial mixer types, respectively Thompson,
 Pressindustria and Fryma mixers.

Table III shows that in each case the inclusion of
 the sodium chloride resulted in an improvement in
 35 effectiveness in inhibiting plaque growth.

TABLE III

5	Toothpaste Pair	Difference in d_o (nm) ¹	Difference in PG values ²
	A,A'	3.5	6.3
	B,B'	3.1	5.6
	C,C'	3.3	4.3
10	1 - the salt-containing toothpastes comprised surfactant liquid crystal phase with smaller d_o values than the respective toothpastes not containing salt		
	² - the salt-containing toothpastes gave lower PG values than the respective toothpastes not containing salt		
15	The amount of the liquid crystal surfactant phase in each of the six toothpastes exceeded 2% by weight.		

Example 3

20

A toothpaste was made from the same ingredients as for toothpaste A of Example 2 save that in place of Triclosan was employed the following antimicrobial agent:-

25

<u>Toothpaste</u>	<u>Antimicrobial agent</u>
D	2,2'-methylenebis(3,4,6-trichlorophenol)

30

Table IV gives the d_o value, percentage weight of the liquid crystal surfactant phase and PG value for the toothpaste.

TABLE IV

5	Toothpaste	d_o (nm)	% wt liquid crystal phase	PG value
	D	4.1	3.7	11.5

10

Example 4

15 This example illustrates the use of further antimicrobial agents.

20 Toothpastes were formulated as for toothpaste C of Example 2, or toothpaste A as indicated, save that the antimicrobial agents listed in Table V were used in place of Triclosan. The lamellar spacings, d_o , of the liquid crystal surfactant phase of each toothpaste is also given in Table V along with the percentage weight of the liquid crystal surfactant phase.

TABLE V

	<u>Antimicrobial Agent</u>	<u>d_o (nm)</u>	<u>%wt liquid crystal phase</u>
5			
	3,4',5-tribromosalicylanilide	4.1	3.0
	3,4,4'-trichlorocarbanilide	4.1	2.4
10	bis(2-hydroxy-5-chlorophenyl) sulphide	4.1	0.8
	5-methyl-2-pentylphenol	4.0	1.7
	2,4-dichlorobenzyl alcohol	4.2	1.6
	4-chloro-3,5-dimethylphenol	4.2	2.0
	5-chloro-2-hydroxydiphenyl methane	3.9	0.9
15	5-n-octanoyl-3'-trifluoromethyl salicylanilide	4.0	2.9
	n-butyl-p-hydroxybenzoate*	3.6	3.8
20	2,2'-methylenebis(4-chloro- 6-bromophenol)*	4.0	4.0

* formulated as for toothpaste A of Example 2

Example 5

25

This example shows that a wide variety of electrolytes can be used to lower the d_o spacing of a liquid crystal surfactant phase of a toothpaste.

30

A series of toothpastes were made having the ingredients of toothpaste C of Example 2 save that the sodium chloride was replaced by another salt as indicated in Table VI below. This table also gives the d_o spacings for the liquid crystal surfactant phase of each toothpaste, and the percentage weight of the liquid crystal surfactant phase.

35

TABLE VI

	<u>Salt</u>	<u>%w/w</u>	<u>d_o</u> (nm)	<u>%wt liquid crystal phase</u>
5				
	Potassium chloride	0.64	3.5	3.6
	Magnesium sulphate 7H ₂ O	2.11	4.5	2.5
	Potassium lactate	1.10	3.6	1.4
10	Potassium tartrate 0.5H ₂ O	1.01	3.7	2.1
	Sodium acetate	0.70	3.5	3.0
	Sodium ascorbate	1.69	3.8	3.2
	Sodium lactate	0.96	3.8	3.0
	Sodium sulphate	0.61	4.2	2.9
15	Trisodium citrate 2H ₂ O	0.84	3.6	3.0
	Potassium gluconate	2.00	3.3	1.7
	Disodium hydrogen orthophosphate 12H ₂ O	1.53	3.9	3.4
	Potassium acetate	0.84	3.6	1.2
20	Sodium glycinate 1H ₂ O	0.98	3.9	2.7
	Sodium gluconate	1.87	3.9	2.2
	Sodium tartrate 2H ₂ O	0.99	4.0	2.2

In each case the amount of salt incorporated was
 25 equivalent to the same molar cation concentration as 0.5%
 sodium chloride.

The d_o values for toothpastes C and C' were 3.9 nm
 and 7.2 nm, respectively.

30

Example 6

This example shows the effect on the lamellar spacing
 of a liquid crystal surfactant phase of a dentifrice of
 35 including increasing amounts of sodium chloride in the
 dentifrice formulation up to 1% by weight of the
 dentifrice. The dentifrice comprised the following
 ingredients.

<u>Ingredients</u>		%
	Alumina trihydrate	50.000
	Sorbitol Syrup (70% solution)	27.000
5	Sodium lauryl sulphate	1.875
	Sodium doceylbenzene sulphonate	0.625
	Sodium carboxymethylcellulose	0.800
	Zinc citrate trihydrate	0.500
	Triclosan	0.200
10	Sodium monofluorophosphate	0.850
	Sodium saccharinate	0.180
	Formalin BP	0.040
	Flavour oil	1.200
	Sodium chloride	see Table
15	Water	To 100.000

The d_o values are given in Table VII together with percentage weights of the liquid crystal phase.

TABLE VII

20	<u>% sodium chloride</u>	<u>d_o (nm)</u>	<u>% wt liquid crystal phase</u>
	0.000	7.5	2.1
	0.100	7.4	2.0
25	0.200	6.4	1.4
	0.300	4.8	1.1
	0.400	4.1	1.0
	0.500	4.1	1.1
	1.000	3.8	1.7

30 All the toothphases were made in the same way, the amount of the sodium chloride being the only variable.

Examples 7 to 11

35 The following are further examples of dentifrice formulations of the invention that have been made.

<u>Ingredient</u>	<u>Example:</u>				
	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>
Alumina trihydrate	50.000	50.000	50.000	50.000	-
Silica xerogel (Gasil 200)	-	-	-	-	10.000
5 Precipitated silica (Sipernat 225)	-	-	-	-	8.000
Sorbitol syrup (70%)	27.000	27.000	27.000	27.000	45.500
Sodium lauryl sulphate	1.875	2.500	1.875	1.875	2.400
Sodium dodecylbenzene sulphate	0.625	0.500	0.625	0.625	0.800
Sodium carboxymethylcellulose	0.850	-	0.800	0.800	0.800
10 Xanthan gum	-	1.000	-	-	-
Zinc citrate trihydrate	1.000	0.500	0.500	-	0.500
Sodium zinc citrate preparation]	-	-	-	2.785	-
Triclosan	0.200	0.120	0.200	0.500	0.200
Sodium chloride	0.500	-	-	-	1.000
15 Titanium dioxide	0.500	1.000	-	-	-
Sodium monofluorophosphate	0.850	1.200	0.850	0.850	1.120
Sodium saccharin	0.180	0.180	-	0.180	0.300
Sodium cyclamate	-	-	2.000	-	-
Formalin BP	0.040	0.040	0.040	0.040	-
20 Flavour oil	1.200	1.200	1.200	1.200	1.200
Colour	0.008	0.007	-	-	-
Water	to 100.000	100.000	100.000	100.000	100.000

1 - an aqueous premix of 1.41% trisodium citrate dihydrate and 1.375% zinc sulphate heptahydrate

	<u>Example:</u>				
	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>
5					
d _o spacing (nm)	4.0	3.9	3.8	3.7	3.5
Plaque growth value	12.7	13.1	-	10.7	-
% wt liquid crystal phase	3.8	2.7	2.6	3.0	10.0

10

Examples 12 to 14

The following are yet further examples of dentifrice formulations of the invention.

15

	<u>Ingredient</u>	<u>Parts by weight</u>		
		Example : <u>12</u>	<u>13</u>	<u>14</u>
	Alumina trihydrate	50.00	50.00	50.00
20	Sorbitol syrup (70%)	27.00	27.00	27.00
	Sodium lauryl sulphate	-	1.50	0.75
	Sodium dodecylbenzene sulphonate	2.00	-	0.75
	Zinc citrate trihydrate	1.00	1.00	1.00
25	Triclosan	0.50	0.50	0.50
	Sodium chloride	1.00	0.50	1.00
	Sodium monofluorophosphate	0.85	0.85	0.85
	Sodium saccharin	0.20	0.20	0.20
	Formalin BP	0.04	0.04	0.04
30	Flavour oil	1.20	1.20	1.20
	Water	9.91	9.90	11.91
	d _o spacing (nm)	3.4	3.8	3.6
	%wt liquid crystal phase	0.3	3.1	2.1

35

Example 15

This example shows that toothpastes having surfactant present in the form of a liquid crystal phase with low d_o spacing result in a superior retention of an antimicrobial agent on the teeth than do toothpastes for which the d_o value is higher.

In this in vitro procedure human molar teeth were used. The area of tooth exposed to the test toothpaste was standardised as follows. Each tooth was cut in half vertically and each half was covered in wax, applied with a camel hair brush, with the exception of a 6mm^2 window left uncovered on the enamel surface of each half tooth.

Toothpastes were delivered as 50% (w/v) slurries prepared freshly on the day of the test as follows. The diluent used was a mixture of ethanol and water (1:2 v/v) with ^3H -Triclosan dissolved to give a final level of Triclosan in the toothpaste/diluent slurry of 20% greater than the total content of the paste being tested. For example, 5g of a formulation containing 2mg Triclosan/g paste (ie 10mg Triclosan) was slurried with 5ml of the ethanol/water mix containing an additional 2mg ^3H -Triclosan.

The volume of the test slurry used in each case was 30 μl ; this was sufficient to cover the tooth window and was applied for 1 minute. After this application the tooth was washed for 45 seconds in water (2ml). The wax was then removed and discarded, and the tooth washed further, twice in ethanol (2ml) for 45 seconds and once in acidified ethanol (2ml:conc HCl/ethanol 1/9 v/v) for 30 minutes. The radioactivity collected in the final two ethanol rinses and in the acid ethanol wash was measured in a Packard Tricarb 4530 Scintillation Counter with

appropriate quench correction, using Insta-gel Liquid Scintillation Cocktail (United Technologies Packard). This was then expressed as the quantity of Triclosan binding to the tooth surface in the exposed window.

5

Appropriate control experiments demonstrated that radioactivity did not penetrate the wax covering of the tooth surface. The binding of Triclosan to the wax was ignored: the wax served simply as a shield and measurement of uptake was by the set area of tooth exposed by the wax window.

10

The results are summarised in Table VIII which represent the mean of nine determinations for each toothpaste.

15

TABLE VIII

	Toothpaste	Triclosan Content (%)	d_o (nm)	Triclosan uptake ($\mu\text{g}/6\text{mm}^2$ tooth surface)
5				
	Example 2A	0.2	4.0	1.36 ± 0.16 *
10	Example 2A'	0.2	7.4	0.87 ± 0.04 *
	Example 1	0.5	4.0	1.28 ± 0.13 **
15	Example 1	0.5	6.3	0.89 ± 0.11 **

* values significantly different at the 5% level

** " " " " " " " "

The batches of toothpastes 2A and 2A' used in this experiment were different from those for which data are given in Table III.

Example 16

This example concerns the finding that the amount of zinc retained in the mouth after use of a toothpaste containing zinc citrate is greater for those toothpastes of which the lamellar spacing of the liquid crystal surfactant phase is the smaller.

Nineteen panellists rinsed an aqueous slurry of toothpaste (1g toothpaste, 4ml water) around the mouth for one minute. After this was expectorated and collected, a one minute 10ml water rinse was carried out and collected. By analysis it was determined what proportion of the zinc in the toothpaste was retained in the mouth after the

rinsing.

The two toothpastes employed had the formulation given in Example 1.

5

The results are given in Table IX.

TABLE IX

10	<u>d_o (nm)</u>	<u>% Zinc Retained in the mouth</u>
	4.0	26%*
	6.3	6%*

15

* values significantly different at the 5% level

Demonstration of long term plaque reduction
and gum health benefit

20

The toothpaste used in this study was that of Table 1 having a d_o spacing of 4.3nm.

25 The effect of the extended use of a dentifrice containing 1% zinc citrate and 0.5% Triclosan on plaque accumulation and gingival health was investigated.

30 The study was divided into two parts, ie. a four-week prestudy period to reduce the influence of motivation and professional cleaning was followed by a ten-week experimental period. During the prestudy period, the participants used a placebo dentifrice which had the same composition as the test toothpaste except that the zinc citrate and Triclosan were omitted. The ten-week
35 experimental period was divided into two four-week periods, separated by a two-week interval. During the

two four-week experimental periods the participants used the test and placebo dentifrices in a double blind crossover design experiment. The two-week interval was adopted in order to minimise the influence of carryover effects.

Volunteers were screened prior to participation in the study. The screening procedure was as follows. The partial recording scheme recommended by Cowell et al in J Clinical Periodontology, 1975, 2, 231-240 was used to select panellists in which the six specific teeth concerned were free of overt caries and had associated pocket depths of less than 3.5 mm when probed using the WHO probe (WHO stands for World Health Organisation). In addition, selected subjects had to exhibit at least a minimal level of gingival inflammation (more than 7 bleeding points out of 24 sites) to allow the demonstration of any improvement. Twenty males and twenty-nine females aged between 23 and 55 years participated in the study. No oral hygiene instructions were given but the participants were encouraged to use sufficient dentifrices to cover the head of the toothbrush (approximately 1.5g).

Plaque was assessed using the Plaque Index according to Silness and Loe (Acta Odont.Scandinavia, 1964. 22, 121-35). Gingival inflammation was assessed by the Gingival Index described by Loe (J. Periodontology, 1967 38, 610-16) and a modification of the Bleeding Index suggested by Cowell et al (J.Clinical Periodontology, 1975, 2, 231-240). Pocket depths were recorded using 0.5 mm graduated plastic strips 1.0 mm in width (Smith, British Dental J., 1975, 139, 369). Assessments were performed on the buccal, mesial, distal and lingual surfaces of representative teeth (2 molars, 2 premolars and 2 incisors) as suggested by Ramfjord (J.

Periodontology, 1959, 30, 51-59).

First, the teeth were professionally cleaned to remove all traces of supra and subgingival plaque and calculus. The participants were then provided with placebo dentifrice and new brushes. The teeth were also professionally cleaned at the second examination which formed the baselines for the first experimental period or the crossover. The Bleeding and Plaque data recorded at this examination were used to allocate the panellist to one of the groups so that two balanced groups were formed (Table X). One group was provided with the test dentifrice and the other group with the placebo, each to be used for four weeks. Following this period, the clinical parameters were reassessed and the placebo dentifrice was used for two weeks to avoid any carryover effects arising from the test dentifrice prior to the second phase of the crossover. Clinical examination and professional cleaning preceded the second experimental phase. Each participant was then given their second dentifrice. Participants were again examined at the end of this period.

The means of the plaque, gingival and bleeding indices for the four-week prestudy period are given below in Table X.

TABLE X

	<u>Plaque Index</u>	<u>Gingival Index</u>	<u>Bleeding Index</u>
Baseline	0.87	1.00	0.47
Four-week	0.77	0.99	0.49

The means of the plaque, gingival and bleeding indices for each four-week experimental period and for the overall

study (n=41) for both dentifrices are given below in Table XI.

TABLE XI

	<u>End of First Experimental Period</u>	<u>End of Second Experimental Period</u>	<u>Mean of Total Group</u>
5			
	<u>Plaque Index</u>		
10			
	Placebo	0.91	0.91
	Test Dentifrice	0.67	0.67
	Stat. signif.P<	0.05	0.001
15	<u>Gingival Index</u>		
	Placebo	0.92	0.92
	Test Dentifrice	0.75	0.73
	Stat. signif.P<	0.06	0.001
20	<u>Bleeding Index</u>		
	Placebo	0.49	0.51
	Test Dentifrice	0.39	0.41
25	Stat. signif.P<	0.09	0.001

The results shown in Table XI demonstrate a significant reduction in plaque accumulation and improvement in gingival health for the test dentifrice compared to the placebo.

Demonstration of enhanced inhibition of plaque metabolism

This study demonstrates that a toothpaste composition according to the invention having a liquid crystal surfactant phase of low lamellar spacing provides an

enhanced inhibition of plaque metabolism compared with one having a liquid crystal surfactant phase of high lamellar spacing. Inhibition of plaque metabolism can be assessed by measuring the pH fall of plaque after a glucose rinse.

5 The toothpastes used in this cross-over study were those of Table I having a d_o spacing of 4.0 and 6.3 nm respectively, and were tested on ten panellists who refrained from toothbrushing for 24 hours prior to the experiment to allow plaque to accumulate. Each

10 participant rinsed for 1 minute with 13 g of a 25% solution of the appropriate toothpaste in water. After 1 hour a plaque sample was collected, comprising of aliquots of plaque removed from at least eight incisor teeth. The pH of this sample dispersed in 5 μ l deionised water was

15 determined using an M1-410 Microcombination pH Probe (Microelectrodes Inc USA), the value being recorded 30 seconds after introduction of the pH electrode. The remaining plaque on the teeth was subjected to a 1 minute rinse with a 15% glucose solution. A second plaque

20 sample was taken 5 minutes later and the pH measured as before. After an interval of 12 days the procedure was repeated with the panellists using the other test product.

The mean values for the pH drop caused by the glucose challenge after use of the test toothpastes are shown in

25 Table XII. The smaller pH drop associated with the use of the product with the smaller d_o value indicates that this toothpaste has a greater effect upon inhibition of

plaque metabolism.

TABLE XII

	d_o spacing of liquid crystal surfactant <u>phase of toothpaste</u>	Mean drop in plaque pH after glucose <u>challenge</u>
5	4.0 nm	0.57*
	6.3 nm	0.84*
10		

* values significantly different at the 5% level.

CLAIMS

1. A dentifrice composition effective to inhibit the growth of dental plaque comprising a surfactant and an
5 anti-plaque agent consisting of a substantially water-insoluble non-cationic antimicrobial agent or a zinc salt having a water solubility greater than 2×10^{-4} g per 100g of water at 25°C and at pH 7, or a mixture thereof, characterised in that there is present in the dentifrice
10 composition a lamellar liquid crystal surfactant phase having a lamellar spacing of less than 6.0 nm in an amount of at least 0.2% by weight of the dentifrice composition.
2. A dentifrice composition as claimed in Claim 1,
15 characterised in that the lamellar spacing of the liquid crystal surfactant phase is less than 4.4 nm.
3. A dentifrice composition as claimed in Claim 1 or Claim 2, characterised in that the lamellar liquid crystal
20 surfactant phase is present in an amount of at least 0.5% by weight of the dentifrice composition.
4. A dentifrice composition as claimed in any of the preceding claims, characterised in that in the formulation
25 of the dentifrice there is also included as an ingredient from 0.1 to 3% by weight of sodium chloride or a water-soluble salt, other than a fluorine-containing salt, in an equivalent molar cation concentration.
- 30 5. A dentifrice composition as claimed in any of the preceding claims, characterised in that in the formulation of the toothpaste there is included 0.1 to 1% by weight of sodium chloride.

6. A dentifrice composition as claimed in any of the preceding claims, characterised in that the anti-plaque agent comprises a mixture of an antimicrobial agent and a zinc salt.

5

7. A dentifrice composition as claimed in any of the preceding claims, characterised in that the antimicrobial agent is Triclosan.

10

8. A dentifrice composition as claimed in any of the preceding claims, characterised in that the zinc salt is zinc citrate.

15

9. A dentifrice composition as claimed in any of the preceding claims, characterised in that the anti-plaque agent consists of a mixture of Triclosan and zinc citrate.

20

10. A dentifrice composition as claimed in Claim 9, characterised in that it comprises 0.05 to 0.3% Triclosan, 0.3% to 1.5% zinc citrate, 0.2 to 1% sodium chloride and 1 to 3% sodium lauryl sulphate.

THIS PAGE BLANK (USPTO)

12

EUROPEAN PATENT APPLICATION

21 Application number: 85303216.7

51 Int. Cl.³: **A 61 K 7/16**
A 61 K 7/24

22 Date of filing: 07.05.85

30 Priority: 09.05.84 GB 8411731

43 Date of publication of application:
21.11.85 Bulletin 85/47

88 Date of deferred publication of search report: 21.09.88

84 Designated Contracting States:
AT BE CH DE FR GB IT LI NL SE

71 Applicant: **UNILEVER PLC**
Unilever House Blackfriars P.O. Box 68
London EC4P 4BQ(GB)

84 Designated Contracting States:
GB

71 Applicant: **UNILEVER NV**
Burgemeester s'Jacobplein 1 P.O. Box 760
NL-3000 DK Rotterdam(NL)

84 Designated Contracting States:
BE CH DE FR IT LI NL SE AT

72 Inventor: **Lane, Roger Michael**
"Underhills" Broad lane
Heswall Wirral Merseyside(GB)

72 Inventor: **Hull, Derek Michael Clarke**
26 Moss Close Willaston
South Wirral Cheshire(GB)

72 Inventor: **Saxton, Charles Allan**
8 Thornton Crescent Gayton
Wirral Merseyside(GB)

72 Inventor: **van der Ouderaa, Franciscus J. G.**
"Kinfauns" 104 Parkgate Road
Neston South Wirral Cheshire(GB)

74 Representative: **Doucy, Robert Henry et al,**
Unilever PLC Patents Division P.O. Box 68 Unilever House
London EC4P 4BQ(GB)

54 Dentifrice compositions.

57 It is disclosed that a dentifrice which includes a surfactant and an anti-plaque agent comprising a substantially water-insoluble non-cationic antimicrobial agent or a zinc salt or a mixture thereof has enhanced activity when the dentifrice comprises at least 0.2% by weight of a lamellar liquid crystal surfactant phase having a lamellar spacing of less than 6.0nm.



European Patent
Office

EUROPEAN SEARCH REPORT

0161898

Application Number

EP 85 30 3216

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	FR-A-2 123 440 (UNILEVER) * Page 4, lines 37-39; examples * ---	1-10	A 61 K 7/16 A 61 K 7/24
D,A	US-A-4 022 880 (VINSON et al.) * Page 5, line 10 - page 9, line 40 * ---	1-10	
D,A	US-A-4 144 323 (LAMBERTI) * Examples * ---	1-10	
A	GB-A-2 052 978 (UNILEVER) * Example 6; claims * ---	1-10	
A	DE-A-3 021 150 (LANGHEIM) * Examples 1,3 * -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 24-06-1988	Examiner GOETZ G.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document			